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(54) **COMBINATION TREATMENT OF PANCREATIC CANCER**

(75) Inventors: **Philip C. Gevas**, Key Biscayne, FL (US); **Dov Michaeli**, Larkspur, CA (US); **Stephen Grimes**, Davis, CA (US); **Martyn Caplin**, London (GB)

(73) Assignee: **Cancer Advances, Inc.**, Durham, NC (US)

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Primary Examiner — Karen Canella
(74) *Attorney, Agent, or Firm* — Jenkins, Wilson, Taylor & Hunt, P.A.

(57) **ABSTRACT**

A combination for use in the treatment of pancreatic cancer comprising:
(i) an anti-gastrin effective immunogenic composition; and,
(ii) one or more chemotherapeutic agents suitable for inhibiting cancer growth.

15 Claims, No Drawings

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COMBINATION TREATMENT OF PANCREATIC CANCER

This application is a continuation of U.S. application Ser. No. 11/360,378, to Philip C. Gevas, Dov Michaeli, Stephen Grimes, and Martyn Caplin, filed Feb. 22, 2006, now abandoned entitled "Combination Treatment of Pancreatic Cancer," which is a continuation of U.S. application Ser. No. 10/104,607, to Philip C. Gevas, Dov Michaeli, Stephen Grimes, and Martyn Caplin, filed Mar. 22, 2002, now abandoned entitled "Combination Treatment of Pancreatic Cancer," which claims the benefit of priority, under 35 U.S.C. §119(e) to U.S. Provisional Application Ser. No. 60/278,294, to Dov Michaeli, Martyn Caplin, Philip Gevas, and Stephen Grimes, filed on Mar. 23, 2001, entitled "COMBINATION TREATMENT OF PANCREATIC CANCER." The subject matter of each of these applications is incorporated herein in its entirety.

FIELD OF THE INVENTION

The invention relates to a combination of immunological and chemotherapeutic treatment of pancreatic cancer. In particular, treatment of locally advanced or metastatic gastrin-dependent pancreatic adenocarcinoma in the form of immunization is provided against gastrin hormone in combination with one or more anti-cancer drugs.

BACKGROUND OF THE INVENTION

In 1998, approximately 29,000 people in the United States were diagnosed with pancreatic adenocarcinoma, and approximately 28,900 people were expected to die from this tumor [1]. The overall cure rate for pancreatic cancer remains less than 5% despite more than 20 years of clinical trials. Only 10% of subjects have a potentially resectable tumor; however, even for subjects undergoing a curative pancreaticoduodenectomy, five-year survival is 6-24% [2]. The vast majority of subjects have unresectable tumors and develop metastatic disease within the first year of therapy. The median survival for subjects with metastatic disease is 3-6 months.

The description of cancertrophic agents set forth below includes both growth factor and growth factor receptors which are surprisingly expressed or overexpressed in cancerous tumors or more specifically cancer cells.

Gastrin is highly expressed in the antral mucosa and duodenal bulb and expressed at low levels in a variety of tissues, including the pancreas. Gastrin is also highly expressed in the fetal pancreas, a fact which may be of significance in the development of pancreatic neoplasms [3].

The normal nonfetal pancreas shows no expression of gastrin isoforms or receptor. It has been shown that a large percentage of patients with pancreatic cancer possess progastrin, glycine-extended gastrin, amidated gastrin in their blood, and CCK-B/gastrin receptor are present in the tumor cells [4]. Thus, it was later found that pancreatic adenocarcinoma expresses the precursor forms of gastrin, especially the progastrin and glycine-extended forms. The tumor cells were also determined to express the CCK-B/gastrin receptor. Similarly, these precursor gastrin forms and receptors were detected in other cancers, such as gastric, colonic, and hepatocellular carcinomas.

Several growth factors have been postulated to affect the growth and development of pancreatic cancer. Moreover, it is well recognized that gastrin is a trophic hormone and promotes growth of gastrointestinal (G1) and non-gastrointestinal cancers [4]. Gastrin has been shown to promote the growth of hepatocellular carcinoma, renal cell carcinoma, small cell carcinoma of the lung and also pancreatic carcinoma [6-9]. Gastrin affects cell behavior in the form of circulating fully processed peptides as well as autocrine process whereby incomplete processed precursor gastrin, especially in the form of glycine-extended gastrin can stimulate cell growth or cell function [10].

In particular, a number of investigations have shown the important role that G17 gastrin and glycine-extended G17 (Gly-G17) gastrin play in the proliferation of gastrointestinal adenocarcinomas including pancreatic adenocarcinoma. It has been demonstrated that G17 gastrin causes proliferation of a variety of colorectal, gastric and pancreatic cancer cell lines, both in vitro and in vivo [11] [12] [6] [13] and that an autocrine pathway may be involved [14] [15]. Gly-G17 gastrin has also been shown to stimulate growth of various cancers via an autocrine/paracrine pathway [16] [17].

Gastrin is actually a family of peptides including G17 gastrin, G34 gastrin, and the immature forms, glycine-extended G17 (Gly-G17) gastrin and glycine-extended G34 (Gly-G34) gastrin. G17 and G34 share a 5-amino-acid carboxy-terminal sequence in common with cholecystokinin (CCK). It has been shown that in this sequence that interacts with the CCK-B/gastrin receptor [11] [18].

Gastrin requires post-translational carboxy-terminal alpha-amidation using glycine as the amide donor. The penultimate intermediate is gastrin with a C-terminal glycine—the so-called glycine-extended gastrins (Gly-G17 and Gly-G34). Similar concentrations of glycine-extended forms and mature gastrins are often found. Gly-G17 appears to have some of gastrin's biological activities [17].

Different tissues exhibit different patterns of post-translational gastrin modification resulting in the accumulation of different intermediates. While gastrin produced by the gastric antrum is largely fully amidated G17 [19], anterior pituitary corticotrophs almost entirely fail to process the amidation site, resulting in >99% glycine-extended gastrins. In neonatal pancreatic cells, gastrin is largely in the G34 form [19] and it is fully sulfated at Tyr29, a unique modification, making it CCK-like in its potency [3]. In neoplastic tissue, immature forms of gastrin typically predominate. In colorectal carcinomas, a considerable amount of progastrin species accumulates [20] [21]. In rat pancreatic tumor AR42J, it has been reported that only glycine-extended gastrins are present [17]. Nothing has been reported on the forms of gastrin produced by human pancreatic cancer cells.

The gastrin and CCK-B receptors were recently cloned and shown to be identical [22]. Messenger RNA for CCK-B receptors was detected in all pancreatic cancer cell lines of ductal origin and in normal pancreatic tissue as well as in fresh tumor cells [23] [24] [25] and may be over-expressed in malignant pancreatic tissue in comparison with normal tissue [26]. Some authors have detected CCK-B receptors using radiolabeled ligand binding (either gastrin or CCK) technologies in both normal pancreas and tumor cell lines [27] Others have failed to detect receptors in the tumor cell lines but do detect them in normal tissue [28] [29].

MacKenzie et al. [30] demonstrated by radioligand-binding the abundant presence of CCK-B/gastrin receptor on the rat pancreatic tumor cell line, AR42J. Tarasova et al. [31] have shown that following ligand binding assays, rapid clustering and internalization of the CCK-B/gastrin receptor occurred in the pancreatic tumor cell line AR42J, as well as in a variety of human gastric and colorectal tumor cell lines. Incubation of the CCK-B/gastrin receptor with 1 nM of the specific inhibitor CI-988 inhibited the proliferation of gastrin-stimulated (1 nM) AR42J cells by about 47% after 96 hours of treatment, which is consistent with competitive inhibition of the gastrin receptor [32]. Anti-G17 antibodies have been shown to inhibit the binding of gastrin to the CCK-B/gastrin receptors on the pancreatic tumor cell line AR42J.

It has been shown that gastrin peptides increase the proliferation of GI cancer cell lines of human and animal origin both in vitro and in vivo [5]. More recent studies with four human pancreatic cell lines have shown that all proliferation was increased by 40-68% G17 gastrin relative to untreated controls. Studies with receptor antagonists showed that this proliferative effect was mediated via the CCK-B receptor [11]. Other studies have reported similar results [12], but not all studies report a positive effect even if the presence of CCK-B receptors was confirmed by binding studies [25].

Additional studies compared the mitogenic effects of gastrin on colorectal and gastric tumor cells obtained from cancer subjects at surgical resection. It was shown that cells from 69% of gastric and 55% of colorectal tumors had an enhanced proliferation in response to G17 gastrin, which was of greater magnitude than that seen in normal cells obtained from the G1 mucosa [33] [34].

It has been shown that the gastrin gene is activated in epithelial cells derived from G1 tumor specimens, but not in normal G1 mucosal cells [35] [36] [37] [21] [17] [38]. Malignant epithelial cells have been shown to produce mitogenic gastrin peptides, which can increase self-proliferation of the surrounding cells, thereby inducing a state of tumor autonomy [39][16].

Gastrin also stimulated in vivo tumor growth in mice inoculated with human Panc-1 cells. Tumor volume in mice treated with pentagastrin was 127% greater than untreated control tumors, while those animals receiving a CCK-B receptor antagonist (without pentagastrin) had tumors only 60% as large as controls [11].

The stimulatory effect of gastrin was also demonstrated by antisense RNA directed at gastrin [40] which suppressed the growth of human pancreatic cell lines. The observation that gastrin mRNA is detectable in all normal as well as tumor cell lines and in fresh pancreatic tissue, while gastrin peptide is detectable only in malignant tissue, suggested that gastrin mRNA may be translated only in the tumor cells [15].

Although inactive in stimulating acid secretion, Gly-G17 gastrin has been shown to increase the proliferation of pancreatic [41] cancer cells, G17 and Gly-G17 were found to be equipotent in stimulating proliferation of rat pancreatic tumor AR42J cells.

The normal physiological functions of gastrin are mediated by CCK-B/gastrin receptors. Expression of the receptor occurs in all types of gastrointestinal malignancies including colorectal, gastric, pancreatic, hepatomas and colorectal liver metastases [42] [43][24] [15] [44] [45] [46]. Different isoforms of the receptor exist [51] [52], and more than one isoform of the CCK-B gastrin receptor may be co-expressed on individual cells. Therefore, antagonism of CCK-B receptors may not be the optimal method to suppress the proliferative action of gastrin present either in the serum or produced locally by the tumor cells.

It has been shown that several types of tumors, e.g., colorectal, stomach, pancreatic and hepatocellular adenocarcinomas, possess CCK-B/gastrin receptors in their plasma membranes and that they respond to gastrin with powerful cellular proliferation [53] [13]. Furthermore, more recently it has been discovered that many of these cancer cells also secrete gastrin and thus effect an autonomous proliferative pathway [21] [37] [16].

The CCK-B/gastrin receptor belongs to a family of G protein-coupled receptors with seven transmembrane domains with equal affinity for both CCK and gastrin [54]. This receptor was named a CCK type-B receptor because it was found predominantly in the brain [55]. The receptor was subsequently found to be identical to the peripheral CCK/gastrin receptor in the parietal and ECL cells of the stomach [56]. This receptor has been well characterized in a number of normal [57] [58] and tumor tissues [59] [34], and extensively studied using the rat pancreatic adenocarcinoma cell line AR42J [60]. The AR42J CCK-B/gastrin receptor cDNA has been cloned and sequenced, and it is more than 90% homologous in DNA sequence to the CCK-B/gastrin receptor in rat and human brain, and more than 84% homologous in sequence to the canine parietal cell CCK-B/gastrin receptor cDNA [61], demonstrating a high sequence homology even between species.

The peptide hormones G117 and G34 bind to the CCK-B/gastrin receptor on the cell membrane of normal cells. However, it has been found that G17, and not G34, stimulates the growth of gastrin-dependent cancer cells. Serum-associated G17, in particular, has the potential to stimulate the growth of colorectal tumors in an endocrine manner mediated by CCK-B/gastrin receptors [34] in the tumor cells. Gastrin-17 appears to be particularly implicated in stimulating the growth of colorectal adenocarcinomas due to a possible increased affinity for the CCK-B/gastrin receptor on the tumor cells, over other gastrin hormone species [62]. The CCK-B/gastrin receptors were found to be expressed in a high affinity form on 56.7% of human primary colorectal tumors [53]. It has been postulated that a potential autocrine loop may also exist due to endogenous production of precursor gastrin peptides by such tumors [21]. The resulting G17 ligand/receptor complex stimulates cell growth by way of secondary messengers for regulating cell function [63]. The binding of G17 to the CCK-B/gastrin receptor leads to activation of phosphatidyl inositol breakdown, protein kinase C activation with a resultant increase in intracellular calcium ion concentration, as well as the induction of c-fos and c-jun genes via mitogen-activated protein kinase, which has been implicated in the regulation of cell proliferation [64]. Additionally, gastrin binding to the CCK-B/gastrin receptor has been associated with the subsequent increase in phosphorylation by a tyrosine kinase, pp125FADK (focal adhesion kinase), which may also have a role in the transmission of mitogenic signals [65].

A number of high affinity CCK-B/gastrin receptor antagonists have been evaluated therapeutically both in vitro and in vivo in a number of experimental models of gastrointestinal cancer. For example, proglumide, a glutamic acid derivative [16] [66] [67] Benzotript, an N-acyl derivative of tryptophan; L-365,260, a derivative of Aspercillin [68], and CI-988 a molecule that mimics the C-terminal pentapeptide sequence of CCK [69] have been shown to effectively neutralize the effects of exogenous gastrin on gastrointestinal tumor growth both in vitro and in vivo [6] [70]. However, these antagonists have severe toxic side effects and lack specificity as they block the action of all potential ligands of the receptor such as G34 and CCK in normal cells. Recently, highly potent and selective CCKB/gastrin receptor antagonists such as YM022 [71] and YF476 [72] have been also described.

Proglumide and Benzotript have been widely assessed in pre-clinical studies. The main problem with these compounds is their lack of potency, with relatively high concentrations required to displace G17. Despite this, proglumide and benzotript inhibited the basal and gastrin-stimulated proliferation of a number of cell lines [67]. In addition, proglumide increased the survival of xenograft mice bearing the gastrin-sensitive mouse colon tumor, MC26 to 39 days in the treated animals from 25 days in the control animals.

Due to the low specificity of this class of gastrin antagonizing agents for the gastrin/CCKB receptor, the inhibition of tumor growth may not be effectively control with gastrin antagonists. Moreover, the cellular receptors which recognize and bind the gastrins do not bind all the inhibitors tested [16]. Thus, if complete inhibition of gastrin binding to the receptor does not occur in the autocrine growth cascade, then the gastrin antagonists may be unable to block this mechanism of tumor growth promotion.

Recent developments have demonstrated the feasibility of immunoneutralization of hormones or their receptor moieties in order to inhibit the hormone controlled physiological functions or effects, such as cellular growth. (U.S. Pat. Nos. 5,023,077 and 5,468,494)

For example, immunization with the immunogen G17DT elicits antibodies that react specifically with the aminoterminal end of G17 gastrin and Gly-G17 gastrin (U.S. patent application Ser. No. 08/798,423). The antibodies do not cross-react with any of the other gastrin species tested, including G34 gastrin and CCK. Antibodies elicited by G17DT inhibit the binding of gastrin to the CCK-B/gastrin receptor on a variety of gastrointestinal tumor cells, including pancreatic tumor cells. Antibodies elicited by G17DT inhibit the growth of human gastric, pancreatic, and colorectal cancer cells in vitro and in in vivo animal models of gastric and colorectal cancer. Immunological neutralization has been discovered to inhibit metastsis of colorectal cancer [46] [47].

The alternate or additional immunological weapon against the gastrin effect on pancreatic cancer growth comprises the induction of anti-CCKB/gastrin receptor antibody binding with a specific anti-receptor GRE1 or GRE4 peptide epitope, as described in co-assigned pending U.S. patent application Ser. No. 09/076,372. Accordingly, the receptor moieties can be prevented from binding the circulating gastrin hormone or fragments thereof. Furthermore, this immunological inhibition of pancreatic cancer advantageously results in the internalization of the receptor antibody complex causing apoptosis-like cell death.

Certain anticancer chemical compounds have been found useful for treating adenocarcinoma such as pancreatic tumors. For example, Gemcitabine (2', 2', difluorodeoxycytidine) is a nucleoside analog with structural similarities to cytarabine. Its mode of action involves disruption of cell replication. Gemcitabine enters the cell via a carrier-mediated transport system that is shared with other nucleosides. It is phosphorylated sequentially to difluorodeoxycytidine monophosphate (diFdCMP), difluorodeoxycytidine diphosphate (diFdCDP) and difluorodeoxycytidine triphosphate (diFdCTP). Preclinical studies of gemcitabine have shown incorporation of the phosphorylated diFdCTP into DNA [73] [74].

Gemcitabine triphosphate is a substrate and competitive inhibitor of DNA polymerases alpha and epsilon. Once dFdCTP is incorporated into the growing chain, only one (or perhaps two) more nucleotide(s) can be incorporated, a novel mechanism termed “masked chain termination.” Once additional residues are incorporated at the 3' end, gemcitabine cannot be excised by the proofreading exonucleolytic activity of DNA polymerase [48]. DNA fragmentation and apoptosis follow. As predicted by its mode of action, gemcitabine is active only in S-phase when cells are actively replicating DNA [49].

Since pancreatic cancer has a high occurrence of metastasis, this method also comprises advantageous combination treatment with immunological anti-gastrin, anti-CCK-B/gastin receptor agents and chemotherapeutic agents such as irinotecan and optionally 5-FU/LV or gemcitabine, or both.

Irinotecan is a chemotherapeutic drug (CAMPOSAR), which has been approved for some types of cancer, mostly as second-live treatment. It has been applied in conjunction with 5-FU/LV against metastatic colorectal carcinoma which progressed after 5-FU treatment.

Cisplatin is a drug used in a variety of neoplasms that is capable of producing inter- and intrastrand DNA cross-links. Cisplatin can be administered alone or together with other chamotherapeucics.

In view of the very poor prognosis of pancreatic cancer and lack of significant survival afforded by the currently available therapies, a therapeutic strategy involving immunological targeting of gastrin and its receptor in combination with chemotherapeutic methods using one or more chemotherapeutic agents may provide a novel and efficacious therapy.

SUMMARY OF THE INVENTION

Contrary to expectations, it has now been discovered that the immune response to vaccination of the treated animal or human is not significantly repressed by chemotherapeutics, or at least can be overcome by adjusting the vaccine dosage.

Advantageously, therefore, the present invention provides a treatment of pancreatic cancer comprising combining immunotherapy with one or more than one anticancer growth active immunogen and chemotherapy wherein the chemotherapy comprises one or more chemotherapeutic anticancer agent.

The invention provides a combination of methods for use in the treatment of pancreatic cancer including metastatic tumors thereof, wherein the immunotherapy is administered both in the form of an active or passive immunological composition comprising one or more cancer trophic target and the chemotherapy comprise one or more chemotherapeutic agent suitable for the inhibition of cancer growth. In the general context of this invention, the active immunization comprises an anti-growth factor immunogen and/or an anti-growth factor receptor immunogen, and the passive immunization comprises anti-growth factor antibodies, and anti-growth factor receptor antibodies which are polyclonal or monoclonal.

In particular, the combination of methods provides treatment of pancreatic cancer by immunological therapy directed against hormones and receptors thereof which stimulate the growth of pancreatic cancer cells, and concomitantly by administration of pharmaceutically acceptable chemotherapeutic agents.

The invention also provides a combination of treatment of pancreatic cancer comprising administering an immunogenic composition containing a conjugate of the amino-terminal G17 peptide epitope covalently linked to an immunogenic carrier proteins and a chemotherapeutic composition.

One form of active immunization according to the invention provides an antigastrin effective immunogenic composition comprising an epitope of the gastrin peptide G17 which is covalently linked through a spacer peptide to an immunogenic carrier or immunogenic carrier fragment.

More particularly, the invention may provide a conjugate of the aminoterminal G17 peptide epitope linked to a seven amino acid peptide spacer, the spacer being attached to an ϵ-amino acid carrying side chain of the lysine residue of diphtheria toxoid and a chemotherapeutic composition carrier protein.

The immunogenic composition according to this invention contains a dosage in units ranging from approximately 10 μg to 5000 μg of immunogen.

An alternate embodiment of the invention provides an antigastrin receptor immunogen. For example, such an embodiment provides an immunogen which comprises a CCKB/gastrin receptor peptide or fragment thereof which elicits antibodies in the immunized patient, wherein the antibodies are specifically directed against an epitope of the receptor so as to bind and inactivate the receptor.

The antibodies produced by the anti-CCK-B/gastrin receptor immunogens thereby inhibit the growth stimulatory pathway, including the autocrine growth-stimulatory pathway of tumor cells and ultimately the growth of the tumor.

Another embodiment of the invention provides an immunogen which elicits an auto-antibody specifically directed to a gastrin receptor, such that upon binding the antibody is internalized into the receptor associated pancreatic tumor cell.

A further embodiment of the invention provides for an immunogen which elicits an antibody specifically directed to the gastrin receptor, or fragment thereof, such that upon binding the antibody is internalized into the nucleus of the receptor associated pancreatic tumor cell.

An embodiment of the treatment of pancreatic cancer provides immunization with an anti-CCKB/gastrin receptor immunogen, alone/or combined with treatment for the cancer by administering a composition comprising one, or more than one, chemotherapeutic agent effective against pancreatic cancer.

A further embodiment of the invention advantageously provides an immunogenic composition formulated as a water-in-oil emulsion amenable for intramuscular injection.

Another embodiment of the treatment of pancreatic cancer provides immunization with both anti-gastrin immunogen and anti-gastrin receptor immunogen combined with one, or more than one, chemotherapeutic agent.

The treatment according to the invention combines the immunological phase of therapy with one or more chemical adjuvant compounds selected from known pharmaceutically acceptable taxanes, such as e.g. docetaxel, taxotere, Paclitaxel, 7-Epi-Taxol, 10-Deacetyl Taxol, as well as mixtures thereof, 5-fluorouracil (5-FU), cisplatin, gemcitabine, irinotecan (also called CAMPOSAR or CPT-11), and tamoxifen 5-FU may be administered with leucovorin.

The chemotherapy comprises doses of 5-FU ranging from 50 to 1000 mg/m^2/d, with leucovorin at 90 mg/d to 100 mg/d or irinotecan ranging from 200-300 mg/m.sup.2/d, gemcitabine ranging from 100-1500 mg/m.sup.2/d; cisplatin (platinol) ranging from 40 mg-100 mg/m.sup.2/d; and tamoxifen from 10 mg-20 mg tablet per day. For example, combinations of chemotherapeutic agents comprise 5-FU Cisplatin, 5-FU-Gemcitabine or 5-FU with leucovorin & cisplatin.

The invention provides a treatment of G17DT immunogen (100-500 μg) in combination with gemcitabine of unresectable metastatic carcinoma of the pancreas in previously untreated subjects.

In accordance with this invention, the method of treatment of pancreatic cancer provides periodic administration of immunological anti-growth stimulating agents in conjunction with a chemotherapeutic agent comprising one or more chemical compounds having an anti-cancer effect. The immunological agents are either hormone immunogens for active immunization or passive immunization with exogenous anti-growth factor antibodies. The exogenous human antibodies can be produced in transgenic animals or other suitable subjects using standard techniques. For passive immunization, the antibodies can be monoclonal, polyclonal or a hybrid. The antibodies are administered in purified form, such as, e.g. IgG fractions, comprising dosages sufficient to neutralize the circulating growth factors or hormones, e.g., gastrin G17 or Gly-G17, or their receptors.

A further growth factor or hormone specific embodiment of the invention utilizes the exogenously added anti-CCKB/gastrin receptor antibody in modified form with agents such as toxins, or radiolabelled substances. The toxin can be of the cholera type. The radiolabel can be ^{125}Iodine, ^{131}Iodine, ^{187}Rhenium or ^{90}Yttrium.

For example, the embodiment provides a radiolabelled specific anti-cancertrophic antibody to destroy the cell upon internalization further in combination with other chemotherapeutic and other immunologically active agents.

Radiolabeled antibodies can also be used for detection diagnoses wherein the radiolabel comprises ^{125}Iodine, ^{131}Iodine, Technetium (T_c), ^{111}Indium, ^{67}Gallium, or ^{90}Yttrium.

DETAILED DESCRIPTION OF THE INVENTION

Anti-G17DT antibodies administered in animals with xenotransplants of various cancers, as well as antibodies elicited by active immunization of subjects with colorectal or stomach cancer with G17DT conjugate, bound both G17 and Gly-G17 gastrins at high affinity. Furthermore, safety and dose ranging studies in subjects with advanced colorectal, stomach, and pancreatic cancers have demonstrated that high-affinity antibodies are elicited by G17DT immunogen. Biological therapies such as immunization with G17DT in combination with chemotherapy may show a higher degree of efficacy than each alone. The higher efficacy is due to the inhibition of a proliferative factor such as gastrin, is cytostatic, and the chemotherapy is a cytotoxic effect. A combination of the two modalities is synergistic, similarly as previously demonstrated with anti-HER2 antibody treatment in combination with chemotherapy in advanced breast cancer [75] and which, more specifically, is shown by results of pre-clinical studies of combinations of G17DT with chemotherapeutic agents.

The majority of neutralizing antisera raised against gastrin peptides has been directed against the 5-amino-acid carboxy-terminal portion of the molecule common to G17 gastrin (SEQ ID NO: 4), G34 gastrin (SEQ ID NO: 5), and cholecystokinin (CCK). This carboxy-terminal sequence of these peptide hormones interacts with the CCK-B/gastrin receptor [14]. G17DT conjugate was developed in an attempt to generate antibodies against the amino-terminal end of G17 and Gly-G17 gastrins. G17DT conjugate is constructed from a synthetic 16-residue peptide comprising an epitope derived from the amino acid residue 1-9 of G17 gastrin linked at the C-terminal to a 7 amino acid residue spacer peptide terminating in a cysteinyl residue. The peptide is cross-linked via its C-terminal cysteine residue to a carrier protein, Diphtheria toxoid (DT), using the bifunctional cross-linker EMCS to form the G17DT conjugate. G17DT has been formulated in a water-in-oil emulsion suitable for intramuscular injection.

Other immunogens for use in the invention are disclosed in the coassigned U.S. Pat. Nos. 5,023,077, 5,488,494; 5,607,676, 5,866,128; 5,609,870; 5,688,506, and 5,662,702 which are incorporated herein by reference in their entirety.

It has been shown that G17-specific antibodies raised, for example, against the instant G17DT immunogen were affinity-purified from rabbit serum and tested for their ability to inhibit in vitro the binding of radioiodinated human G17 to AR42J cells, a rat pancreatic cancer cell line that expresses gastrin receptors. It was shown that the anti-G17 antibodies, pre-mixed with the labeled G17, significantly (>90%) inhibited the binding of G17 to the cells. This data demonstrate their capacity of the antibodies to neutralize the biological activity of human G17 in pancreatic cancer cells.

G17DT does not cause significant systemic side effects, and no evidence has been found for deleterious effects of long-term neutralization of G17 gastrin and Gly-G17 gastrins. The only significant side effect following immunization-with G17DT is injection site reactions.

Neutralization of the endocrine and autocrine/paracrine effects of G17 and glycine-extended G17 gastrin is proposed as a mechanism by which G17DT immunization can reduce gastrin-stimulated tumor growth, and increase survival of the patient. A G17DT formulation has been developed that elicits an immune response while exhibiting an acceptable local reactogenicity.

Furthermore, as described in the co-assigned international patent application serial number PCT/US99/10750, anti-gastrin immunization treatment combined with lower than normal amounts of Leucovorin/5-FU, has been advantageously effective.

The methods of the invention are directed to the treatment of gastrin hormone-dependent tumors in animals, including humans, and comprise administering to a patient an anti-CCK-B/Gastrin-receptor immunogen, which induces the formation of antibodies in the immunized patient which bind to the CCK-B/gastrin-receptor on the tumor cells. Antibodies bound to the cell receptors block the binding of the hormone to the receptor and thereby inhibit the growth promoting effects of the hormone. More importantly the receptor/anti GRE1 (anti-gastrin receptor epitope 1) antibody complex is rapidly internalized, traverses the cytoplasm and enters the nucleus. The complex one in the nucleus triggers the affected tumor cells to commit suicide (apoptosis).

The immunogens of the invention comprise natural or synthetic peptides of the human CCK-B/gastrin-receptor which act as immunomimics. In particular, two synthetic peptides have been developed as the immunomimics. These peptides, developed from the amino acid sequence of the CCK-B/gastrin-receptor, are immunogenic and cross-reactive with the endogenous CCK-B/gastrin-receptor of tumor cells both in vivo and in vitro. Peptide 1 consists of amino acids 5 through 21 of the CCK-B/gastrin-receptor sequence KLNRSVQGTGPGPGASL (Peptide 1, SEQ ID NO.: 1 in the Sequence Listing). Peptide 1 constitutes part of the amino-terminal domain of the receptor and is located on the extracellular surface of the cell membrane.

In another embodiment, the immunogen comprises Peptide 4, which consists of the amino acid sequence of the CCK-B/gastrin-receptor: GPGAHRALSGAPISF (Peptide 4, SEQ ID NO.: 2 in the Sequence Listing). Peptide 4 is part of the fourth extracellular domain of the receptor and it too is on the outer side of the cell membrane.

The immunogens may also comprise an extension or spacer peptide suitable for projecting the immunomimic peptide away from the protein carrier and to enhance its capacity to bind the lymphocyte receptors. A suitable spacer peptide has the amino acid sequence SSPPPPC (Serine (Ser) spacer, SEQ ID NO.:3 in the Sequence Listing). However, other spacer peptides would be suitable as well. The immunomimic peptides, with or without the spacer, are then conjugated to a protein carrier, such as Diphtheria toxoid, via a cysteine residue at the carboxy terminal end. The spacer peptides are not immunologically related to the CCK-B/gastrin-receptor-derived peptides and should therefore enhance, but not determine, the specific immunogenicity of the receptor-derived peptides.

The presence and density of CCK-B/gastrin-receptors on tumor cells in a patient can be determined in vitro by reacting labeled anti-receptor antibodies with a sample of obtained from a tumor biopsy. The anti-receptor antibodies can be labeled with either a radioactive tracer, a dye, an enzyme or a fluorescent label, as known in the art. In addition, the responsiveness of the tumor cells to gastrin can be evaluated in vitro from a tumor biopsy sample of the patient using standard techniques. Patients having tumor biopsy samples positive for the CCK-B/gastrin-receptor antibody assay are typical candidates for treatment by the methods of the invention.

An effective dosage ranging from 0.001 to 5 mg of the immunogenic composition is administered to the patient for the treatment of the gastrointestinal cancer. The effective dosage of the immunogenic composition should-be capable of eliciting an immune response in a patient consisting of effective levels of antibody titer against the CCK-B/gastrin-receptor 1-3 months after immunization. Following the immunization of a patient, the effectiveness of the immunogens is monitored by standard clinical procedures, such as ultrasound and magnetic resonance imaging (MRI), to detect the presence and size of tumors. The antibody titer levels against the receptor may also be monitored from a sample of blood taken from the patient. Booster immunizations are given as required to maintain an effective antibody titer. Effective treatment of gastrin-dependent cancers, such as stomach, liver, pancreatic and colorectal adenocarcinomas, according to this method should result in inhibition of tumor growth and a decrease in size of the tumor.

The antibodies raised by the anti-CCK-B/gastrin-receptor immunogens of the present invention may have anti-trophic effects against gastrin-dependent tumors by three potential mechanisms: (i) inhibition of gastrin binding to its receptor, (ii) degradation or disruption of the signal transduction pathway of tumor cell proliferation; and (iii) induction of apoptosis (or cell suicide) in cells where receptor/antibody complexes are internalized and migrate into the nucleus.

In another embodiment of the invention, anti-CCK-B/gastrin-receptor antibodies are administered to a patient possessing a CCK-B/gastrin-receptor-responsive tumor. The antibodies specifically bind to the CCK-B/gastrin-receptors on the tumor cells. The binding of the antibodies to the receptors prevents the binding of gastrin to its ligand in the membranes of cells and, therefore, the growth signal for the gastrin-dependent tumor cells is inhibited and the growth of the tumor is arrested. The antibodies are preferably chimeric or humanized antibodies, or fragments thereof, which effectively bind to the target receptor and may be produced by standard techniques, such as, e.g., those disclosed in U.S. Pat. Nos. 5,023,077, 5,468,494, 5,607,676, 5,609,870, 5,688,506 and 5,662,702. These exogenously produced antibodies may also be useful for killing tumor cells that bear the CCK-B/gastrin-receptor on their plasina membranes by virtue of their inhibiting the growth of the tumor cells or delivering a toxic substance to the tumor cell. Therapeutic anti-CCK-B/gastrin antibodies are those reactive with extracellular domains 1 and 4 of the receptor protein as GRE-1 and GRE-4, respectively. The inhibition of tumor growth in this method of immunization is also monitored by ultrasound imaging and MRI and repeated immunizations are administered as required by the patient.

The effectiveness of the antibodies in inhibiting tumor cell growth and killing of tumor cells can be enhanced by conjugating cytotoxic molecules to the anti-CCK-B/gastrin antibodies and the anti-gastrin G17 or G17-gly antibodies. The cytotoxic molecules are toxins, for example, cholera toxin, ricin, α-amanitin, or radioactive molecules labeled, for example, with ^{125}I or ^{131}I, or chemotherapeutic agents, as for example, cytosine arabinoside or 5-fluorouridine (5-FU).

In addition to antibodies radiolabeled with ^{125}I and ^{131}I, the anti-CCK-B/Gastrin-receptor antibodies can also be labeled with radionuclides such as [111]Indium and [90]Yttrium. In this aspect of the invention, the antibodies are useful for the detection and diagnosing of CCK-B/gastrin-receptor possessing tumors in vivo, by administering these antibodies to the patient, and detecting bound antibodies on CCK-B/gastrin-receptor-containing tumor cells. After allowing the radio labeled anti-CCK-B/gastrin antibodies to reach the tumor, about 1-2 hours after injection, the radioactive, "hot spots" are imaged using standard scintigraphic procedures as previously disclosed (Harrison's Principles of Internal Medicine, Isselbacher et al. eds. 13th Ed. 1994).

The compositions in which the immunogens are administered for the treatment of gastrin-dependent tumors in patients may be in a variety of forms. These include, for example, solid, semi-solid and liquid dosage forms, such as tablets, powders, liquid solutions, suspensions, suppositories, and injectable and infusible solutions. The preferred form depends on the intended mode of administration and therapeutic applications. The compositions comprise the present immunogens and suitable pharmaceutically acceptable components, and may include other medicinal agents, carriers, adjuvants, excipients, etc. Suitable adjuvants may include nor-muramyl dipeptide (nor-MDP, Peninsula Labs., CA), and oils such as Montanide ISA 703 (Seppic, Inc., Paris, France), which can be mixed using standard procedures. Preferably, the compositions are in the form of a unit dose. The amount of active compound administered for immunization or as a medicament at one time, or over a period of time, will depend on the subject being treated, the manner and form of administration, and the judgment of the treating physician.

The anti-CCK-B/gastrin-receptor antibodies of the invention for passive immunization can be administered to a patient intravenously using a pharmaceutically acceptable carrier, such as a saline solution, for example, phosphate-buffered saline.

The pharmacology and toxicology for the instant combined treatment of advanced pancreatic cancer is described below:

Example A

G17DT was administered to 28 patients with advanced pancreatic adenocarcinoma at weeks 0, 1 and 3 at a 250 µg dose [16]. Only one patient failed to mount an antibody response. G17DT was well tolerated with no systemic side effects. One patient developed a sterile abscess that settled following aspiration. Survival was found to be significantly improved in G17DT patients when compared to an historical control matched in terms of age, stage and co-existing morbidity by POSSUM scoring [40].

Concerning the response rates of subjects with pancreatic cancer the median time to onset of the immune response to G17DT appears to be dose related and to be optimal at ≧250 µg G17DT.

Example B

The immuno-electronmicroscopy studies used an antiserum directed against the amino-terminal end of the CCK-B/gastrin-receptor (GRE-1 epitope) show that after one hour incubation, the distribution of immunogold-label CCK-B/gastrin-receptor antibody was quickly internalized as 12% of the antibody receptor complex was associated with the cell membrane, 36.6% within the cytoplasm, 7.9% in the nuclear membrane and, quite surprisingly, 43.5% within the cell nucleus. Areas of intense CCK-B/gastrin-receptor immunoreactivity within the nucleus were found on chromatin, which may suggest specific binding sites for regulation of the DNA.

These electron microscopy studies with anti-immunoglobulin conjugated to gold beads (immunogold) reveal that an extremely rapid turnover of the anti-receptor/receptor complex occurs in the tumor cells; as early as 10 seconds after exposure to antibodies, complexes are detectable in the cell nucleus.

Example C

Immunological Efficacy

Patients' sera were assessed for antibodies to G17 gastrin at 2-4 weekly intervals. Anti-gastrin-17 antibodies were measured using a titration and inhibition radioimmunoassay with ^{125}I labeled human gastrin-17. Assays for antibodies to G17 gastrin in the pancreatic cancer trials 1 and 2 have been performed by a G17 antigen-based ELISA.

The pharmacodynamics of the immune response to G17DT was evaluated as a function of the dose and treatment regimen for G17DT. The frequency of seroconversion and time to onset of production of G17 gastrin-specific antibodies was used to estimate the optimal dose.

A positive immune response in test serum by RIA was defined as being ≧40 fold above non-specific background determined on a 1:40 dilution of pre-immune subject serum within the first 12 weeks post-immunization. This corresponds to approximately 10% of total ^{125}I G17 cpm added in the RIA assay. A positive response in the ELISA assay approximates ≧4 units in the ELISA assay which is comparable to that observed by RIA.

To facilitate comparison of doses and formulations, the immune response up to and including the 12-week time point observed in subjects with non-resectable, locally advanced (stage II/III) and metastatic (stage IV) pancreatic cancer were used to determine the proportion of immune responders among the treatment groups in the various studies. The proportion of immune responders and the median time to develop an immune response are summarized in Tables A and B, respectively.

A dose finding phase II study of G17DT in 22 patients with pancreatic carcinoma demonstrated greater survival in patients who mounted an adequate antibody response when compared to non-responders (7.89 versus 4.93 months) [39].

TABLE A

Immune response in subjects with Stage II-IV pancreatic cancer

Study		Studies 1&2 (Stage II-IV)		
G17DT Dose	Schedule	n	$N^{a,b}$	%
10 µg	0, 4, 8 wk	—	—	—
10 µg	0, 2, 6 wk	—	—	—
100 µg	0, 4, 8 wk	—	—	—
100 µg	0, 2, 6 wk	5	13	38
165 µg	0, 4, 8 wk	—	—	—
250 µg	0, 4, 8 wk	—	—	—
250 µg	0, 2, 6 wk	6	10	60
250 µg	0, 1, 3 wk	—	—	—
330 µg	0, 4, 8 wk	—	—	—
330 µg	0, 2, 6 wk	—	—	—
330 µg	0, 2, 10 wk	—	—	—

TABLE A-continued

Immune response in subjects with Stage II-IV pancreatic cancer

Study G17DT Dose	Schedule	Studies 1&2 (Stage II-IV) n	$N^{a,b}$	%
495 μg	0, 4, 8 wk	—	—	—
990 μg	0, 4, 8 wk	—	—	—
Total		11	23	48

n = number of subjects with an immune response.
N = number of subjects (immune responders and non-responders) that have completed 12 weeks
% = (n/N) × 100
[a]In study 1, 4 subjects have not completed 12 weeks (evaluation ongoing).
[b]In study 2, 11 subjects have not completed 12 weeks (evaluation ongoing); no immune response data available.

TABLE B

Time to immune response in subjects with Stage II-IV pancreatic cancer

Study G17DT Dose	Schedule	1^a & 2^b (Stage II-IV) Median (weeks) ± SD
10 μg	0, 4, 8 wk	—
10 μg	0, 2, 6 wk	—
100 μg	0, 4, 8 wk	—
100 μg	0, 2, 6 wk	10 ± 1
165 μg	0, 4, 8 wk	—
250 μg	0, 4, 8 wk	—
250 μg	0, 2, 6 wk	6 ± 3
250 μg	0, 1, 3 wk	—
330 μg	0, 4, 8 wk	—
330 μg	0, 2, 6 wk	—
330 μg	0, 2, 10 wk	—
495 μg	0, 4, 8 wk	—
500 μg	0, 4, 8 wk	
990 μg	0, 4, 8 wk	—
Mean		8 ± 2

[a]In study 1, 4 subjects have not completed 12 weeks (evaluation ongoing).
[b]In study 2, 11 subjects have not completed 12 weeks (evaluation ongoing); no immune response data available.

Chemotherapy

Example 1

Activity of Gemcitabine

The US FDA approved gemcitabine for use in pancreatic cancer based on the results from several clinical trials [GEMZAR (gemcitabine HCl) package insert, 1996, 1998, summarized in Table 3]. Subjects with locally advanced or metastatic disease were treated with gemcitabine 1000 mg/m^2 weekly×7, or ×3, followed by one week of rest, then weekly×3 every four weeks thereafter. Early Phase II trials indicated that a significant number of subjects experienced some palliation of symptoms despite only modest objective response rates. To quantitate these effects, a novel end point termed Clinical Benefit Response was developed for use in subsequent trials.

Clinical Benefit Response is a composite of degrees of pain (analgesic consumption and pain intensity), Kamofsky performance status, and weight change. Gemcitabine was the first agent to be approved using clinical benefit response as an endpoint. Clinical benefit required a sustained (≧4 weeks) improvement in at least one parameter without worsening in any others. Subjects were considered clinical benefit responders only if they showed at least a 50% reduction in the level of pain (Memorial Pain Assessment Card) or consumption of pain medication, or at least a 20-point improvement in performance status (Karnofsky Performance Scale) for a period of at least four consecutive weeks, without showing any sustained worsening in any of the other parameters. A subject was also considered a clinical benefit positive responder if stable in all these parameters.

Example 2

Therapy with Gemcitabine

Prior to the approval of gemcitabine (GEMZAR, Eli Lilly & Co.) in 1996 for the first-line treatment of locally advanced and metastatic adenocarcinoma of the pancreas, 5-fluorouracil (5-FU) had been the standard of G1 or pancreatic cancer care for 30 years. A review [50] of 28 Phase II trials involving 25 new agents showed that none provided any improvement over 5-FU in subject outcome, with a median objective response rate of 0% (range 0-14%) and a median survival of 3 months (range 2-8.3 months). Suggestions that combined chemotherapeutic treatments offered improvements over 5-FU alone were not confirmed in randomized Phase III trials [50].

Gemcitabine exhibits several self-potentiation mechanisms which enhance its incorporation into DNA [76]. These effects are mediated via interactions of gemcitabine and its metabolites with the enzymes of pyrimidine nucleotide metabolism and are believed to be significant in producing the high concentration of active drug in cells and in prolonging the half-life of active drug in cells. These include the following:

Gemcitabine triphosphate directly inhibits dCMP deaminase, thus inhibiting the breakdown of gemcitabine monophosphate to difluorodeoxyuridine monophosphate (the major breakdown pathway)

Gemcitabine triphosphate may also inhibit CTP synthase, which catalyzes the synthesis of CTP from UTP and ammonia (or glutamate), additionally depleting dCTP pools.

Inhibition of ribonucleotide reductase by gemcitabine diphosphate reduces the concentrations of dCTP and dCDP, both of which feedback inhibit deoxycytidine kinase. Thus, more gemcitabine is phosphorylated because the feedback inhibition is removed.

Gemcitabine has also been shown to be a potent radiosensitizer. This activity does not parallel the incorporation of the phosphorylated drug into DNA. Rather, it parallels the intracellular depletion of dATP, suggesting that the inhibition of ribonucleotide reductase is the key mechanism of this action [73] [74] [1]. In general, agents (e.g. urea) that reduce dNTP pools act as radiation sensitizers. The intermediate diFdCDP (gemcitabine diphosphate) is a potent inhibitor of ribonucleotide reductase. This inhibition causes a decrease in all four deoxynucleotide triphosphate intracellular pools, which results in an inhibition of DNA synthesis. Variation in the extent of depletion of each dNTP pool in different cell types suggests that the greater depletion of the dATP pool in particular observed in solid tumor cell types may account for the greater clinical activity of gemcitabine in solid tumors [74] [1].

Gemcitabine rapidly distributes into total body water after IV administration. The volume of distribution is affected by duration of infusion, age, and sex. Longer infusions result in higher concentrations.

Clearance is independent of dose and duration of infusion but is variable, and is influenced by age. Because the volume of distribution increases with longer infusion times, its elimination half-life is longer when it is infused over a longer period.

Gemcitabine is deaminated by cytidine deaminase in plasma to difluorodeoxyunridine, which is inactive. Only 5% is excreted unchanged as gemcitabine.

Gemcitabine is generally less well tolerated than 5-FU, but despite a higher incidence of adverse events, its overall toxicity is considered moderate. There is no evidence of cumulative toxicity.

A treatment of the invention combines immunoneutralization of G17 gastrin or G17-Gly gastrin with the chemotherapy with gemcitabine. The advantageous aspect of this combination affords a lower dosage of gemcitabine or irinotecan (or some similarly amenable and approved anti-cancer drug) such that the toxicity and other adverse side effects are reduced. In addition, the immunization with, e.g., G17-DT immunogen containing compositions, can be administered at a time preceding the chemotherapy in order to avoid suppressing of the immuno response before a sufficient titer of auto-antisera has been raised in the treated subject.

Example 3

Therapy with Irinotecan

Irinotecan injection (irinotecan hydrochloride injection) is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as Camptotheca acuminata. The chemical name is (S)-4,1-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxi-[H-pyrano[3',4':67]-indolizino[1,2-b] quinolin-9-yl-[1,4'-bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. It is supplied as a sterile, pale yellow, clear, aqueous solution. Each milliliter of solution contains 20 mg irinotecan. (The Camptosar package insert provides detailed labeling information for irinotecan). Irinotecan is an emetogenic. Therefore patients may receive premedication with antiemetic agents. Irinotecan therapy had been shown to cause G1 adverse effects, in particular early and late diarrhea. Early diarrhea may be accompanied by cholinergic symptoms. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. Late diarrhea should be promptly treated with loperamide. In addition to the G1 manifestations, irinotecan has been shown to cause myelosuppresion and hypersensitivity reactions. Only patients with adequate hematologic, renal, and hepatic function, as well as patients with no contraindication to irinotecan from previous irinotecan-based therapy, are able to avoid or immunize the frequency and severity of toxic effects such as neutropenia and G1 abnormalities.

Patients are permitted to remain on the medications they are taking except for immunosuppressants, including systemic (i.e., oral or injected) corticosteroids. All concomitant medications should be recorded on the appropriate page of the CRF.

Palliative radiotherapy is allowed. In the event that gemcitabine therapy is terminated because of a SAE, G17DT immunization can be continued.

Example 4

Therapy with Cisplatin

Injections with Platinol, a solution of cisplatin or cis-diammine dichloroplatinual II, is used mostly in combination with other cytotoxic agents has used as a potential cure of testicular germ cell neoplasms. Substantial activity has been observed in the treatment of small cell lung cancer, bladder cancer and ovarian germ cell tumors. According to the invention, cisplatin may augment antipancreatic cancer treatment in combination with other pharmaceutically acceptable cytotoxic agents and immunogens or exogenous application of anti-cancertroph antibodies. Suitable effective dosing may range as high as 1000 mg/m^2 per week although the chemotherapeutic effect may be enhanced with simultaneous immunotherapy so as to allow lower chemotherapeutic dosages.

Example 5

Effect of Gemcitabine on G17DT Immunogenicity

The example depicts an in vivo test to assess the effect of the chemotherapeutic agent Gemcitabine on the immunogenicity of the G17DT immunogen. For that purpose, as a model animal system, mice were immunized intraperitoncally (IP) with 125, 250 and 500 μg doses of G17DT in Montanide ISA 703 emulsions of 0.1 ml volume on days 0, 28 and 56. Gemcitabine was given intravenously (IV) at a dose of 21.4 mg/kg in a volume of 0.2 ml on days 0, 7, 14, 21, 28, 35, 42, 56, 63 and 70. Control mice received saline vehicle without the chemotherapeutics. The resultant anti-G17 antibody responses were measured by ELISA in sera collected every two weeks, and one bleed at day 21, over the course of the study.

The G17DT immunogen was formulated under sterile conditions using PBS (physiological saline solution) as diluent. The emulsion was produced by mixing the agueous phases of immunogens with Montanide ISA 703 at an oil: aqueous phase w/w ratio of 70:30.

Aliquots 8-10 mg dry Gemcitabine were weighed to be solubilized in PBS at a human treatment concentration of 3.424 mg/ml Gemcitabine before i.v. administration.

The results of the treatment over the course of 84 days showed that all mice responded to G17DT immunogen with similar kinetics comparing the median responses of all groups. (see Table 1).

Mice immunized with 125 μg G17DT manifested a statistical decrease in mean anti-G17 titers when concomitantly treated with Gemcitabine. However, the suppression was overcome by increasing the dose of immunogen to 250 μg or 500 μg G17DT.

This second part of the example depicts cell proliferation of human pancreatic cell lines, PANC-1, BxPC3 and PAN-1 using a tetrazolium-based combined with anti-gastrin G17 antibodies induced by G17DT (10-500 μg/ml). The G17DT elicited antibodies are active against both serum-associated and tumor-secreted, proliferative forms of gastrin. The PAN-1 cell were administered at clinically reflective doses.

G17DT concentrations of 100 and 50 μg/ml increased the in vitro inhibitory effects of Gemcitabine (1.0-0.01 μg/ml) by 11-38% ($p<0.05$, ANOVA) when compared to the individual agents for all three cell lines.

In vivo G17DT alone inhibited basal pancreatic tumor weight by 33% ($p=0.016$, ANOVA) compared to 38% for Gemcitabine ($p=0.004$, ANOVA). When combined the agents inhibited tumor weight by 55% which was significant from G17DT alone ($p=0.025$). Thus the immunological agent G17DT may promote the therapeutic efficacy of Gemcitabine.

TABLE 1

Mean Anti-G17 Titer ± Standard Error Plus Student's t-Test								
	DAY OF STUDY							
	0	14	21	28	42	56	70	84
Group 1; 125 μg G17DT Placebo Treatment	0	1.006 ± 240	1.132 ± 140	1.227 ± 210	74.780 ± 7.655	40.200 ± 4.883	241.140 ± 37.905	95.940 ± 23.248
Group 2; 125 μg G17DT Gemcitabine Treatment	0	292 ± 59	408 ± 77	408 ± 104	43.860 ± 11.118	21.497 ± 6.813	64.200 ± 18.788	37.774 ± 9.480
t-test Group 1 vs. 2 P(T <= t) two-tail		0.020[1]	0.002[1]	0.008[1]	0.051[1]	0.054[1]	0.003[1]	0.049[1]
Group 3; 250 μg G17DT Placebo Treatment	0	2.047 ± 717	2.074 ± 575	2.349 ± 622	86.840 ± 34.076	25.913 ± 8.730	71.788 ± 21.755	42.166 ± 13.013
Group 4; 250 μg G17DT Placebo Treatment	0	923 ± 242	1.899 ± 724	2.863 ± 1.284	169.300 ± 65.955	40.620 ± 11.494	256.560 ± 59.743	73.220 ± 17.674
t-test Group 3 vs. 4 P(T <= t) two-tail		0.176	0.855	0.728	0.299	0.338	0.020[1]	0.195
Group 5; 500 μg G17DT Placebo Treatment	0	1.555 ± 160	4.703 ± 963	6.489 ± 1.545	107.398 ± 26.096	43.146 ± 13.699	196.000 ± 44.006	118.667 ± 50.824
Group 6; 500 μg G17DT Placebo Treatment	0	1.100 ± 452	1.715 ± 790	4.372 ± 2.127	653.925 ± 360.669	162.900 ± 90.679	166.800 ± 87.853	77.450 ± 13.846
t-test Group 5 vs. 6 P(T <= t) two-tail		0.370	0.043[1]	0.436	0.130	0.184	0.760	0.407

[1]Statistical significance at $p \leqq 0.05$

Another embodiment of the present invention provides treatment with more than one chemotherapeutic agent in combination with active immunization against an appropriate growth factor and/or growth factor receptor. For example, such treatment can involve a combination of 5-FU/Leucovorin or 5-FU plus cisplatinum.

As a preclinical experiment, mice were treated with a combination of the two anticancer agents 5-FU and Cisplatinum and tested as to the extent of numerous suppressive effects.

Example 6

Effect of 5-FU & Cisplatinum on G17DT Immunogenicity

This example concerns the effect of co-treatment with the chemotherapeutic agent 5-fluorouracil (5-FU) and Cisplatinum (II)— Diamine Dichloride (Cisplatinum as the active ingredient of the drug formulation cisplatin) upon the immunogenicity of G17DT immunogen in mice.

G17DT immunogen was formulated with MONTANIDE ISA 703 at 1.25 mg/ml of G17DT conjugate. Mice were immunized intraperitoneally (IP) with an injection volume of 0.1 ml delivering a dose of 125 μg G17DT on days 0, 28 and 56. The chemotherapeutic dosing regimen was based on the doses recommended for human patients. Thus the combined 5-FU plus Cisplatinum was administered to the test group on day 0, following by 5-FU above on days 1 and 2 by intravenous injection in 0.2 ml volume at doses of 10.0 mg/kg 5-FU and 1.0 mg/kg Cisplatinum. Control mice were immunized while receiving saline vehicle without the chemotherapeutics. As supportive therapy for the potential dehydration caused by Cisplatinum, all mice received IP 1.0 ml PSS (Physiological Saline solution). The anti-G17 antibody levels in sera collected at 14-day intervals (plus an additional on d 21) were assayed by ELISA.

The G17 DT immunogen was formulated as described in Example 4. The 5-FU and Cisplatinum formulations were prepared at 10.0 mg/kg for 5-FU and 1.0 mg/kg for Cisplatinum to provide calculated doses of 320 mg of 5-FU and 32 mg of Cisplatinum. The dry aliquots of 5-FU and Cisplatinum were reconstituted on treatment days by dissolution in the same PSS to yield 1.6 mg/ml and 0.16 mg/ml, respectively. For day 1 and 2, 5-FU alone was given at 1.6 mg/ml in PSS.

The subject mice were ten CAPF1 female, about 18 months old. All mice were G17-immunized at a dose (IP) of 0.1 ml of G17 DT on days 0, 28, 56 of study. All chemotherapeutics were administered in volumes of 0.2 ml. Control mice received 0.2 ml of PSS placebo, according to the treatment regimen. To counter Cisplatinum related dehydration, all mice were injected IP with 10 ml PSS per mouse. The mice were bled every 14 days starting on day 0 and ending on day

84. The sera were assayed by ELISA, showing that all mice responded to G17 DT immunogen with significant titers of anti-G17 antibodies. The responses of both groups peaked on day 70. The mean/median response of the combination treatment group was overcome by the administration of the second injection of immunogen. The results indicate that the 5-FU plus Cisplatinum treatment (following a dose regimen designed for humans) had no statistically significant negative effect on the anti-G17 antibody response.

The treatment(s) can be administered up to disease progression, unacceptable toxicities or withdrawal of consent. If the unacceptable toxicities are due to chemotherapy and the subject's disease has not progressed, chemotherapy can be stopped and immunotherapy can be continued as planned. Immunotherapy is continued after the onset of disease progression and is stopped only for unacceptable toxicity attributable to G17DT or withdrawal of consent.

TABLE 2

A Comparison of Anti-G17 Antibody Mean Titers by ELISA (Ex. 6) (plus/minus S.D.)

	DAY OF STUDY							
	0	14	21	28	42	56	70	84
Group 1, 125 μg	100	997 ± 194	1.099 ± 249	1.029 ± 355	70.660 ± 30.571	48.020 ± 22382	108300 ± 44771	50500 ± 11449
Group 2, 125 μg G17DT, 5-FU-CISPLATINUM Treatment	100	874 ± 222	739 ± 265	266 ± 83	81.400 ± 34429	35.966 ± 14014	15.4360 ± 41771	48.860 ± 10797
t-test Group 1 vs. 2 P(T <= t) two-tail		0.687	0.351	0.066	0.821	0.660	0.473	0.920

Example 7

A. Combined Treatment with Immunization and Gemcitabine (Protocol)

The following clinical treatment regime is provided:

MEDICATION	G17DT	Gemcitabine
(immunotherapy + chemotherapy)	Days 1, 28, 56	Day 1 and continue once a week for a total of 7 weeks, followed by 1 week rest. Then continue with 4-week cycles of 3 weekly administrations, followed by 1 week rest each cycle.

Sampling Schedules:

Blood Chemistry:	weekly
Hematology:	weekly
Urinalysis:	weekly
Immunology:	bi-weekly to week 12, monthly after week 12

Diagnostics Prior to Entry:

Endoscopy:	pre-enrollment
CT scan and Chest x-ray:	pre-enrollment

Diagnostics Follow Up:

CT scan:	monthly
Chest x-ray:	as needed

Gemcitabine

Dose:	1000 mg/m^2
Route:	in 250 ml of 0.9% sodium chloride over 30 min., IV infusion
Schedule:	Day 1 and continue once a week for a total of 7 weeks, followed by 1 week rest. Then continue with 4-week cycles of 3 weekly administrations, followed by 1 week rest each cycle.

Alternatively, the dosage of gemcitabine may be reduced to about 750 mg/m^2 or 500 mg/m^2 or less.

B. Combination with Irinotecan

Irinotecan was initially approved as second-line therapy for patients with metastatic colorectal carcinoma whose disease has recurred or progressed following 5-FU-based therapy. Subsequently, irinotecan in combination with 5-FU and LV was approved as first-line therapy for treatment of this disease. Irinotecan-based therapy, however, is not without significant morbidity, including diarrhea and myelosuppression. To reduce these side effects, dose adjustments are often necessary that may reduce the efficacy of irinotecan. Patients who fail irinotecan-based therapy, thereby, are left with few options for the efficacious treatment of their disease.

Immunotherapy combined with irinotecan has the potential to enhance overall therapeutic effect, while reducing side effects associated with irinotecan treatment. In addition to having antitumor activity on its own, gastrin neutralization by G17DT administered prior to 5-FU and LV treatment has been shown to enhance the antitumor activity of 5-FU and LV therapy, and potentiated the activity of suboptimal doses of 5-FU on rat colorectal tumors.

Using this rationale, it can be proposed that G17DT may also potentiate the efficacy of irinotecan and offer a potentially new treatment modality that combines the cytostatic action of antigastrin immunization with the cytotoxic effects of chemotherapy. In addition, immunization with G17DT could be used with drugs whose maximum doses must be reduced due to associated serious AEs.

G17DT is administered as an intramuscular injection of 250 μg in 0.2 ml, vehicle. To elicit an immune response, G17DT is administered in the initial treatment period at Week 1. In the absence of Grade 2 or greater allergic reaction to G17DT following first injection of G17DT, additional doses of G17DT are administered at Weeks 5, 9; thereafter G17DT is administered following a decrease in anti-G17 titer of 50% or more from the maximum titer.

Irinotecan is administered as an intravenous infusion of 125 mg/m^2 over 90 minutes starting at Week 5 or 4 weeks after the initial administration of G17DT. Each cycle of treatment consists of irinotecan i.v. administration by infusion once weekly for 4 weeks, followed by a 2-week rest period. Additional cycles of treatment are repeated until disease progression, dose limiting toxicity (DLT), or patient withdrawal. If necessary, doses of irinotecan can be adjusted by using specific dose modification rules to accommodate individual patient tolerance of treatment. In the absence of DLT or progressive disease, patients continue the G17DT-irinotecan combination treatment regimen. This dosing regimen is based on results from 3 open-label, single-agent clinical studies involving a total of 304 patients.

Example 7

Tumor Response Criteria

Abdominal/pelvic CT scan with IV contrast and chest x-ray (as needed) can be used to assess tumor burden.

Examples of such lesions evaluated by clinical examination or imaging tools include:

a skin nodule or superficial lymph node minimum≧10 mm×≧10 mm

a liver lesion, soft tissue, lymph node and masses investigated by CT scan (minimum≧20 mm×≧10 mm).

These include all the lesions that can be measured with only one diameter ≧20 mm on CT scan or ≧10 mm on physical examination.

An example of these lesions is a palpable abdominal mass or soft tissue mass that can be measured only in one diameter.

Example 8

Evaluation of Response

Subjects must have received 3 immunizations with G17DT and/or GRE1DT and a minimum of one 7-week cycle or two 4-week cycles of treatment with gemcitabine with at least one follow-up tumor assessment using the same method as baseline to be considered evaluable for response unless "early progression" occurs, in which case they are considered evaluable (in progressive disease). Subjects on therapy for at least this period have their-response classified according to the definitions set out below.

Immune response assessments is made by ELISA on blood samples collected from subjects every 2 weeks up to 12 weeks and every 4 weeks thereafter. Tumor assessment for all lesions must be performed every 4 weeks on therapy until the documentation of the progression. Tumor-response should be reported on follow-up visits every 4 weeks for the subject who goes off study for reason other than progressive disease (PD).

No further anti-tumor therapy is given after end of treatment until disease progression is documented, except if the subject requests further therapy or the investigator deems it necessary. All uni- or bi-dimensionally measurable lesions should be measured every subsequent 4 weeks. Additional assessments should be performed to confirm a response at least 28 days after the first response has been observed. In addition, extra assessments may be performed if there is a clinical suspicion of progression. When multiple lesions are present, this may not be possible and, under such circumstances, up to 6 measurable target lesions which are representative of all organs involved should be selected for the involved sites, giving the priority to bi-dimensionally measurable lesions, then uni-dimensionally measurable lesions.

Best overall response is the best response designation recorded from the start of treatment until disease progression.

Complete and partial responses have to be confirmed by two evaluations of the disease, taken at least 4 weeks apart (see above for assessment time).

No change is only accepted if it is measured at least 4 weeks after the treatment start.

Tumor response, time to progression, time to treatment failure and survival can be analyzed both on an intent-to-treat basis and on the evaluable population.

The period for complete response lasts from the date the complete response was achieved to the date thereafter on which progressive disease is first noted. In those subjects who achieved partial response, only the period of overall response should be recorded. The period of overall response lasts from the day of the first observation of response (partial or complete) to the date of first observation of progressive disease.

Time to disease progression is the time measured from the start of treatment to the first progression, death, or discontinuation of both chemotherapy and immunotherapy, whichever occurs first. Subjects that have not progressed at the time of the final analysis can be censored at the date of their last tumor assessment. Subjects who receive non-study anti-tumor therapy before disease progression can be censored at the date of the last assessment before therapy.

Time to treatment failure is the time measured from the start of treatment to the date of failure (progression, relapse, death or any other cause of treatment discontinuation).

Survival is measured from the start of treatment to the date of death from whatever cause. Subjects alive as of the final analysis will be censored at their last contact date.

The pharmacodynamics of the immune response following the primary series of three injections are assessed by the proportion of immune responders with ≧4 ELISA units sustained for 2 consecutive bleeds in study Arm A attained by week 12 following the first immunization and by the mean and median peak titers. Immunoassays are performed by G17 antigen-based ELISA. The quality of the antibody response is measured by inhibition RIA and assessed by dissociation constant (Kd) and antigen binding capacity (ABC), and ABC/Kd ratio.

The mean and median duration of the immune response from peak titer to <25% of peak titer is assayed in order to determine the time to administer a booster immunization.

Taxanes

Recent treatments of advance prostate cancer include the administration of chemotherapeutic agents such as taxanes. Taxanes, such as, for example, docetaxel, are effective microtubule inhibitors thereby interfering in the further transition of the cell cycle at G2/M check-point. Taxanes have now emerged as a promising class of newly approved chemotherapies currently under investigation in hormone-refractory prostate cancer. A number of recent studies indicate that the taxane, i.e. docetaxel, is particularly active. For example, 35 patients with hormone-refractory prostate cancer were treated with docetaxel at 75 mg/m^2 every 21 days while being maintained on androgen suppression. Toxicity remained tolerable throughout the treatment; although there were two deaths during the study, one due to lung toxicity/pneumonia and one due to pulmonary embolus. Responses, defined as a more than 40% PSA decline and a more than 50% reduction of bi-dimensional cross-products in patients with measurable disease, were seen in 17 of the 35 patients enrolled, including one complete response. Responses were maintained for a median of nine months (range, 2 to 24 months). The median overall survival in this study was 27 months. Preclinical studies suggested a potential benefit for the combination of docetaxel with estramustine in the treatment of patients with hormone-refractory prostate cancer. Based on data from two phase I studies, the docetaxel dose applied for phase II study which was undertaken in combination with estramustine in human subjects was 70 mg/m^2 or 60 mg/m^2. Phase II studies of docetaxel plus estramustine have demonstrated more than 50% PSA declines in 59% to 88% of patients. Although reduction of the dose of estramustine appears to result in a somewhat lower response rate, the contribution of estramustine to the efficacy of the docetaxel-estramustine combination was not conclusive.

Passive Immunization:

The chemotherapies described above can be combined with passive immunization against cancer growth promoting factors and receptors comprises administration of purified antibodies which can be polyclonal or monoclonal. Monoclonal antibodies are conventionally prepared for treatment in humanized or chimeric form.

The transgenic mouse isolated human antibodies can be further modified by radiolabel or other toxic materials so as to induce necrosis or apoptosis in the target cancer cells. For example, the antibodies, modified or not, will be directed to bind to receptors, many of which will internalize the ab-receptor complex to the nucleus of the cell so as to lead to the affected cell's death, which process may be similar or like apoptosis. Pancreatic carcinoma treatment can include one or more of the combinations of chemotherapeutic agents and active or passive immunotherapies, as described above. However, the treatment are not in any way limited to the specific aforementioned samples. On the contrary, the thrust of the invention suggests a useful variety of combined chemical and immunological agents to slow or decrease tumor growth.

Polyclonal antibodies can be obtained from immunized human and other mammalian sources. One manner of inducing high affinity specific antisera utilizes the immunogen as described above where the antigenic varieties are conjugated to immunogenic carrier. The highly active antibody fractions are isolated and purified by conventional means for inoculation in the cancer patient in need of this treatment. Since this type of passive immunotherapy can utilize the patient's own antibodies, the risk of rejection and other complications can be minimized or entirely avoided.

Treatment with modified, such as radioactive-labeled antibodies is from anti-CCKB/gastrin receptor antibodies would effect cell death by internalized specific irradiation. Furthermore, the combination therapy using gastrin and gastrin receptor immunogens can be administered to immunize or prevent metastasis of gastrin-dependent adenocarcinoma cells. Such metastatic cancer cells may derive from gastric, prostate, pancreatic, or colorectal lesions and localize in other tissues, such as bone, liver, or lymph nodes. Anti-gastrin immunization has been shown to inhibit liver metastasis.

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The invention claimed is:

1. A combination for use in the treatment of pancreatic cancer comprising:

(i) an anti-gastrin effective immunogenic composition;

(ii) an anti-CCKB/gastrin receptor peptide effective immunogenic composition, wherein the anti-CCKB/gastrin receptor peptide comprises SEQ ID NO: 1 or SEQ ID NO: 2; and

(iii) one or more chemotherapeutic agents selected from the group consisting of a pharmaceutically active taxane, gemcitabine, and irinotecan.

2. The combination of claim 1, wherein the anti-gastrin effective immunogenic composition is selected from immunogens comprising an epitope of the gastrin peptide G17 covalently linked through a spacer peptide to an immunogenic protein or fragment thereof.

3. The combination of claim 1, wherein the anti-gastrin effective immunogenic composition comprises a conjugate of an aminoterminal G17 peptide epitope covalently linked to a seven amino acid residue peptide spacer which is attached to an ϵ-amino side chain of an immunogenic carrier protein lysine residue.

4. The combination of claim 1, wherein the anti-CCKB/gastrin receptor peptide effective immunogenic composition comprises a conjugate of SEQ ID NO: 1 attached to an ϵ-amino side chain of an immunogenic carrier protein lysine residue.

5. The combination of claim 4, wherein the amount of immunogen in the anti-gastrin effective immunogenic composition is about 250 μg to 500 μg per dose.

6. The combination of claim 1, wherein the anti-gastrin effective immunogenic composition is formulated in a water-in-oil emulsion suitable for intramuscular injection.

7. The combination of claim 1, wherein the amount of immunogen in the anti-gastrin effective immunogenic composition ranges from 10 μg to 5000 μg of the immunogen per dose.

8. The combination of claim 1, wherein the chemotherapeutic agent is gemcitabine.

9. The combination of claim 1, wherein the amount of immunogen in the anti-gastrin effective immunogenic composition is about 250 μg to 500 μg per dose.

10. The combination of claim 1, wherein the chemotherapeutic agent is irinotecan.

11. A combination for use in the treatment of pancreatic cancer comprising:

(i) an anti-gastrin effective immunological agent, wherein the anti-gastrin effective immunological agent is a monoclonal antibody or polyclonal antibodies derived from antisera produced in a patient by immunization with an anti-gastrin immunogenic composition;

(ii) an anti-gastrin receptor effective immunological agent, wherein the anti-gastrin receptor effective immunological agent is a monoclonal antibody or polyclonal antibodies derived from antisera produced in a patient by immunization with an anti-gastrin receptor immunogenic composition, and further wherein the anti-gastrin receptor immunogenic composition comprises an anti-CCKB/gastrin receptor peptide comprising SEQ ID NO: 1 or SEQ ID NO: 2; and

(iii) one or more chemotherapeutic agents selected from the group consisting of a pharmaceutically active taxane, gemcitabine, and irinotecan.

12. The combination of claim **11**, wherein the chemotherapeutic agent is gemcitabine.

13. A method for treating pancreatic cancer in a patient, comprising administering to the patient a gastrin-immunoneutralizing immunogenic composition, wherein the immunogenic composition comprises an immunogen directed to eliciting neutralizing antibodies against a CCK-B/gastrin receptor peptide comprising SEQ ID NO: 1 or SEQ ID NO: 2; and administering to the patient a pharmaceutical composition of one or more chemotherapeutic agents selected from the group consisting of a pharmaceutically active taxane, gemcitabine, and irinotecan.

14. The method of claim **13**, wherein the chemotherapeutic agent is gemcitabine.

15. The method of claim **13**, wherein the patient has metastatic pancreatic cancer.

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